REMARKS

The Office Action has been carefully reviewed. Claims 13-16, 20-22, 30, 43-50, 52-60, and 62-71 presently appear in this application with claims 52-54 and 65-68 indicated as being allowed. Reconsideration and allowance of all the pending claims are hereby respectfully solicited.

Claims 13-16, 20-22, 30, 43-50, 55-60, 62-64 and 69 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The examiner states that, due to the limited structural information regarding what amino acid residues may be deleted, substituted or inserted into the polypeptides according to the present invention, wherein said polypeptide retains the ability to bind TRAF2 and inhibit or increase the activity of NF-kB, and the level of unpredictability associated with protein structure and predicting protein function and the lack of guidance thereof in the specification as filed, it is concluded that applicant's disclosure is insufficient to adequately describe the genus of polypeptides encompassed by the claimed invention. The examiner takes the position that, with the exception of the amino acid sequences according to SEQ ID NO:2, and amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:6, or the amino acid sequence of SEQ ID NO:5, applicant's specification does not provide sufficient description for the broad genus of

polypeptides encompassed by the instant claims since possession cannot be shown by providing a means to isolate a compound. What is required according to the examiner is an actual description of the claimed invention, particularly by means of drawings or structural chemical formulas that show that the invention was complete at the time of filing of the claimed invention. This rejection is respectfully traversed.

Accordingly to applicants' understanding of the agreement reached at the face-to-face interview in March 2001, applicants believe that claim 62 and claims dependent therefrom were mistakenly included in this rejection. The Examiner's Interview Summary (Paper No. 26) states:

> It was agreed that in view of the functional language, and scope of claims 62-63, the pending rejection under 35 U.S.C. 112 should be removed. However, the remaining claims must be reviewed in regard to 35 U.S.C. 112 first paragraph issue in view of the fact that these claims recite substitutions, deletions, and insertions of more than one amino acid (emphasis added).

From the discussion at the interview, applicants believe that claims 62-63, which recite for only a single amino acid substitution, insertion or deletion, comply with 35 U.S.C. §112, first paragraph, for both enablement and written description and are not subject to this rejection.

To address this lack of written description rejection insofar as it relates to more than one amino acid change and fragments, the examiner's attention is respectfully drawn to the Revised Interim Written Description Guidelines Training Materials and, particularly, Example 14: "Product-by-Function". In that example, the specification

exemplified a protein isolated from liver that catalyzed the reaction of A→B, which isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO:3. The specification also contemplated, but did not exemplify, variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions, and additions. The specification indicated that procedures for making proteins with substitutions, deletions, insertions, and additions is routine in the art and provided an assay for detecting the catalytic activity of the protein.

This description in the specification is very similar to the description which appears in the present specification. The present specification exemplifies a polypeptide that binds to TRAF2 and either inhibits or increases the activity of NF-kB. The sequence of this polypeptide is specified. The specification contemplates, but does not exemplify, variants of the protein wherein the variant can have substitutions, deletions, insertions, and additions. The present specification also indicates that procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art (see, for example, substitute specification, bottom of page 34 to page 38) and provides an assay for determining whether any given protein binds to TRAF2. See, for example, the yeast two-hybrid method in the Materials and Methods section of the Examples, i.e., pages 91-94, and the *in vitro* assays of Example 3 and 4, pages 101-105.

In Example 14 of the Training Materials, the claim is directed to:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B.

The present claim 69 is drawn to a polypeptide that includes an analog having no more than ten changes in the amino acid sequences recited in a) and b) of claim 69 and has the ability to bind to TRAF2 and either inhibits or increases the activity of NF-kB. The amino acid sequences of SEQ ID NO:2 and SEQ ID NO:5 recited in claim 69(a) are 604 and 417 residues in length, respectively. Therefore, analogs with no more than ten amino acid changes would be at least 95% identical to the amino acid sequences recited in claim 69(a).

The analysis in the Training Materials acknowledges that procedures for making variants of SEQ ID NO:3 are conventional in the art and that an assay is described which will identify other proteins having the claimed functionality. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity were conceded as being conventional in the art. It would, of course, be understood that procedures for making analogs/variants of the polypeptide of SEQ ID NO:2, of SEQ ID NO:5, or that encoded by the nucleotide sequence of SEQ ID NO:6, which have no more than ten amino acid changes in the sequence and retain binding activity to TRAF-2 as well as functional activity of either inhibiting or increasing the activity of NF-kB are also conventional in the art.

The analysis goes on to point out that all variants of the claim must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO:3. Furthermore, because of the "comprises" language, the protein claimed may be larger than SEQ ID NO:3 or its variant with 95% identity to SEQ ID NO:3. The analysis points out that the specification contains a reduction to practice of the single disclosed species. The analysis concludes:

> The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variations since all the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO:3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.
>
> Conclusion: The disclosure meets the requirements of 35 USC §112, first paragraph, as providing adequate written description for the claimed invention.

Thus, it is apparent that if the single species disclosed is representative of the genus and an assay is present for identifying the members of the variants which are capable of the specified functionality, the written description requirement is met, regardless of the protein chemistry arguments made by the examiner.

It would not require undue experimentation to test any given analog with no more than 10 amino acid changes to determine if it retains the properties of binding to TRAF2 and of either inhibiting or increasing the activity of NF-kB.

As to the "fragment" portion of the claim, it would be expected that if one amino acid were removed from the C-terminus that the fragment which remains will still be active. It is within the skill of the art to remove one amino acid at a time from either end of a protein or an analog, and then run the assay to determine if the fragment retains functionality. Once a fragment loses functionality, then it is not necessary to test any further. This does not involve

undue experimentation. Thus, because any such fragment must have a portion of the specified sequence and a simple assay is readily available, as is a rational means to determine which fragments would be expected to be operable, the full sequence, representing the single species of the presently claimed polypeptide and its functional fragments, is representative of the genus. One of ordinary skill would thus conclude that applicants were in possession of the necessary common attributes possessed by the members of the genus. Therefore, the requirements of 35 U.S.C. §112, first paragraphs, as to providing adequate written description for the claimed invention are met.

Reconsideration and withdrawal of this rejection are, therefore, respectfully requested.

New dependent claims 70 and 71, as fully supported by Tables 1A and 1B on pages 40-41 of the substitute specification are added.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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Version with Markings to Show Changes Made

Claims 49 and 55 have been amended as follows:

49 (Thrice-amended). A method for identifying and producing a molecule capable of directly or indirectly either inhibiting or ~~decreasing~~increasing the cellular activity which is changed or mediated by a polypeptide according to claim 69 comprising~~,~~:

a) screening for a molecule capable of directly or indirectly either inhibiting or increasing the cellular activity which is changed or mediated by a polypeptide according to claim 69;

b) identifying and characterizing said molecule; and

c) producing said molecule in substantially isolated and purified form.

55 (Thrice-amended). A DNA sequence encoding a polypeptide ~~that binds to TRAF2 and either inhibits or increases activity of NF-κB~~in accordance with claim 69, selected from the group consisting of:

(i) a cDNA sequence comprising the nucleotide sequence of SEQ ID NO:1;

(ii) a cDNA sequence comprising the nucleotide sequence of SEQ ID NO:6;

(iii) a cDNA sequence comprising the nucleotide sequence of SEQ ID NO:4;

(iv) a fragment of a sequence of (i)-(iii) which encodes a polypeptide that binds to TRAF2 and either inhibits or increases the activity of NF-κB;

(v) a DNA sequence capable of hybridization to a sequence of (i)-(iv) under moderately stringent conditions and which encodes a polypeptide that binds to TRAF2 and either inhibits or increases the activity of NF-κB; and

(vi) any DNA sequence other than those defined in (i)-(v) which encodes a polypeptide in accordance with claim ~~51~~69.